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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/214,679	12/30/1999	WALTER BRIEDEN	A32213-PCT	8348

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ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	09/214,679	BRIEDEN ET AL.
	Examiner Manjunath N. Rao, Ph.D.	Art Unit 1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 14 January 2003.

2a) This action is **FINAL**.      2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 28-44 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 28-44 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some \* c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_.

4) Interview Summary (PTO-413) Paper No(s) \_\_\_\_\_.

5) Notice of Informal Patent Application (PTO-152)

6) Other: \_\_\_\_\_

## **DETAILED ACTION**

Claims 28-44 are still at issue and are present for examination.

Applicants' amendments and arguments filed on 1-14-03, paper No.21, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 35 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. See previous Office action.

In response to the previous Office action, applicants cancelled claims 22-27 to overcome the above rejection. However, they have not addressed the rejection of claim 35. The above rejection is maintained by the Examiner.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 41 and 43 are rejected under 35 U.S.C. 102(a) as being anticipated by Hirrlinger et al. (J. Bacteriol., June 1996, Vol. 178(12):3501-3507). This rejection is based upon the public availability of a printed publication in this country before the invention by the applicant for a patent. Claims 41 and 43 of the instant application are drawn to a biologically pure culture of microorganism wherein said microorganism utilizes/hydrolyzes propionamide of formula VI in the form of the racemate or of its optically active isomers as the sole nitrogen source and wherein the microorganism is selected from the group consisting of *Rhodococcus*, *Arthrobacter*, *Bacillus*, *Klebsiella* and *Pseudomonas*, or a cell extract of such microorganisms. Hirrlinger et al. disclose the pure culture and cell extract of one such microorganism, *Rhodococcus* MP50 which use as sole nitrogen source or hydrolyzes enantioselectively a wide range of aliphatic and aromatic amides (see the entire document). Therefore Hirrlinger et al. anticipate claims 41 and 43 of this application as written.

Applicants argue that Examiner has not provided a reference which teaches every element of the rejected claims and that the reference does not explicitly teach that the microorganism in the reference uses the propionamide of formula VI (containing no aryl groups) as sole nitrogen source or that it hydrolyzes the propionamide of formula VI. However, this argument is not persuasive to overcome the rejection because Hirrlinger et al. disclose that the above microorganism hydrolyzed a wide range of aliphatic and aromatic amides even though hydrolysis of specific aliphatic amides may not be disclosed. While applicants argue that the compound of the formula VI does not have aryl groups, and hence the reference does not apply,

such an argument is not persuasive to overcome the above rejection because the reference discloses that the microorganism has the capability to hydrolyze a wide range of both aliphatic (groups in which there are no double bonds) and aromatic amides. Therefore, the compound of formula VI which does contain aliphatic group (CH<sub>3</sub>) encompasses the amides disclosed in the reference. Based on the characteristic feature of the microorganism to use aliphatic amides as sole source of nitrogen and also based on its ability to hydrolyze the above compound, Examiner takes the position, that the microorganism inherently has the characteristic of using or hydrolyzing the propionamide of formula VI even though the reference does not explicitly teach the same. Since the Office does not have the facilities for examining and comparing applicants' microorganism with the microorganism of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the microorganism of the prior art does not possess the same material structural and functional characteristics of the claimed microorganism). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

In response to the previous Office action applicants have traversed the above rejection arguing that Hirrlinger et al. does not disclose a microorganism that utilizes the propionamide of formula VI, which lacks an aryl group. Applicants also argue against the position taken by the Examiner based on the concept of inherency. Applicants point out that the compound with formula VI does not have a aryl group and therefore, the reference of Hirrlinger et al. does not anticipate above claims contrary to the position taken by the Examiner based on inherency. While Examiner agrees with the applicants that the compound with formula VI lacks an aryl group, he would like to draw the attention of the applicants to the fact that the microorganism

in the reference has the capacity to hydrolyze a wide range of amides which includes aliphatic amides. While the reference may not specifically disclose the hydrolysis activity of the microorganism on the specific compound with formula VI, such a compound is encompassed by the phrase "aliphatic amides". Therefore, contrary to applicants argument, the above reference does anticipate claims 41 and 43 as written.

Claims 41 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Dominique et al. (EP 433117 A1, 10-6-1991). This rejection is based upon the public availability of a printed publication in this country more than one year prior to the date of application for patent in the United States. Claims 41 and 43 of the instant application are drawn to a biologically pure culture of microorganism wherein said microorganism utilizes/hydrolyzes propionamide of formula VI in the form of the racemate or of its optically active isomers as the sole nitrogen source and wherein the microorganism is selected from the group consisting of *Rhodococcus*, *Arthrobacter*, *Bacillus*, *Klebsiella* and *Pseudomonas*, or a cell extract of such microorganisms. Dominique et al. disclose the pure culture and cell extract of one such microorganism, *Rhodococcus* species which hydrolyzes propionamides (see the entire document). While the reference does not explicitly disclose that the bacterial species hydrolyzes the propionamide with formula VI, Examiner takes the position that the microorganism disclosed in the reference does so, based on the broad interpretation of the phrase that the microorganism in the reference is capable of "enantioselective synthesis of acids from racemic amides (and in particular propionic acids)" (see page 2 first paragraph) to encompass all types of propionamides

including those with the formula VI. Therefore Dominique et al. anticipate claims 41 and 43 of this application as written.

Applicants argue that Examiner has not provided a reference which teaches every element of the rejected claims. Applicants argue that the reference does not explicitly teach that the microorganism uses the racemate forms of propionamide of formula VI as sole nitrogen source or that it hydrolyzes the same. However, this is not persuasive to overcome the rejection because, based on the characteristic feature of the microorganism to hydrolyze propionamides which encompasses all types of propionamides, the hydrolysis of the compound with formula VI would be an inherent characteristic of the above microorganism. Examiner has considered the phrase “enantioselective synthesis of acids from racemic amides and in particular propionic acids” broadly and takes the position that the compound with formula VI is encompassed in the above phrase. Examiner concludes that the amidase enzyme isolated from the microorganism in the reference and the enzyme referred to in the application are the same. Since the Office does not have the facilities for examining and comparing applicants’ microorganism with the microorganism of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the microorganism of the prior art does not possess the same material structural and functional characteristics of the claimed microorganism). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 28-34, 36-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hirrlinger et al. (as applied to claims 41, 43 or Dominique et al. as applied to claims 41-44 above, and further in view of Keith et al. (EP 524781 A1, 1-27-1993). Claims 22-34, 36-44 of the instant application are drawn to a biologically pure culture of microorganism wherein said microorganism utilizes/hydrolyzes propionamide of formula VI in the form of the racemate or of its optically active isomers as the sole nitrogen source and wherein the microorganism containing a polynucleotide (with SEQ ID NO:1 or any polynucleotide which hybridizes to SEQ ID NO:1 under stringent conditions and encodes a stereospecific amidohydrolase) encoding a polypeptide with SEQ ID NO:2, having amidohydrolase activity and wherein such activity hydrolyzes the propionamide of the formula VI, is selected from the group consisting *Rhodococcus, Arthrobacter, Bacillus, Klebsiella and Pseudomonas*, a cell extract of such microorganisms and the use of such microorganisms or their cell extract for the preparation of the compounds of the formula I, II, VII, VIII by converting propionamide of the formula VI followed by their isolation.

The references of Hirrlinger et al. and that of Dominique et al. have been discussed above.

Keith et al. teach that compounds with the formula R-3,3,3-trifluoro-2-hydroxy-2-methylpropionamide are useful as cell potassium channel openers in humans and certain substituted amides are useful in treatment of urinary incontinence. The reference also teaches that because above compounds function to open potassium channels, they may also be useful as therapeutic agents in the treatment of conditions or diseases in which opening of potassium channels of the cells leads to amelioration of associated disorders such as hypertension, asthma, peripheral vascular disease, heart failure, angina, baldness, premature labor, impotence, peptic ulcer etc. Thus it appears that the above group of compounds are very important pharmaceuticals. There is also information in the art that chemical synthesis of above group of compounds is a very expensive venture and that there is a concerted effort in the art to make these compounds by cost effective methods.

With the teachings of all the above references in hand, it would have been obvious to one of ordinary skill in the art to use the microbiological approach by identifying microorganisms capable of providing the basic compound that can be further derivatized depending on the ultimate therapeutic use or isolate the cDNA and the enzyme produced by such microorganisms and use them in place of the microorganisms. Methods for isolation of the cDNA that encodes said enzymes and/or purification of said enzymes or recombinant enzymes are well within the ability of those skilled in the art. Based on the teachings of Hirrlinger et al. or Dominique et al. one skilled in the art would have been motivated to use the microorganisms (or the enzymes produced by such microorganisms produced by using the cDNA) disclosed in those references to make the compounds for the ultimate use taught by Keith et al. One of ordinary skill in the art would have been motivated to do so as Keith et al. teach that such compound have therapeutic

effects towards to a wide range of human disorders. One of ordinary skill in the art would have a reasonable expectation of success since the references of Hirrlinger et al. and Dominique et al. provide the microorganisms that make the enzyme required for the making the product taught by Keith et al.

Therefore the above invention is rendered *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office action, applicants have traversed the above rejection arguing that the propionamide of formula VI does not have an aryl group and also that there is no motivation or suggestion to use the propionamide of formula VI, which lacks an aryl group and therefore would not have been obvious. While Examiner acknowledges that the compound with formula VI lacks an aryl group, one skilled in the art would expect microorganisms of the references to act on precursors of compounds taught by Keith et al., in view of the broad specificity shown and therefore it would have been obvious to one of ordinary skill in the art to use the microorganisms to produce the compounds of Keith et al. While the reference does not explicit refer to the hydrolysis of compound with formula VI, the reference also does not exclude the hydrolysis of compound with formula VI by the reference microorganisms. This is because the reference reads on all “enantioselective synthesis of acids from racemic amides and in particular propionic acids” and especially aryl propionamides. While the reference exemplifies an arylpropionamide, it does not in any way exclude propionamides with the formula VI but encompasses all types of propionamides including those with the formula VI. Therefore for all the above reasons, Examiner maintains the above rejection.

***Conclusion***

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.



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1600

Manjunath N. Rao Ph.D.  
Patent Examiner, A.U. 1652  
March 18, 2003